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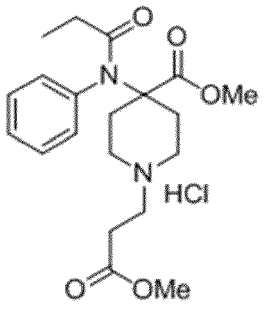
(54) NEW INTERMEDIATES FOR THE PREPARATION OF REMIFENTANIL HYDROCHLORIDE

(57) A new intermediate for synthesizing 1-substituted-4-[phenyl(propanoyl)amino]piperidine-4-carbonitrile derivatives is laid open. Specifically set out is a method for use of this intermediate in the preparation of remifentanil. The enclosed shorter process offers a greater yield of products with higher purity as compared to methods reported in the prior art.



Remifentanil hydrochloride

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EP 3 643 704 A1

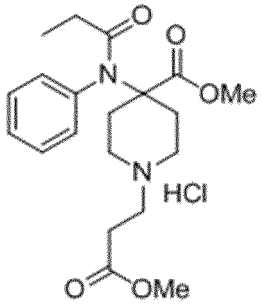
Description

Field of invention

[0001] The present invention relates to a process for the synthesis of fentanyl-type opioid analgesics. In particular, the present invention describes a new efficient synthetic route for the preparation of Remifentanil hydrochloride and precursors thereof.

State of the art

[0002] Remifentanil hydrochloride (1, Figure 1) belongs to the 4-anilidopiperidine class of synthetic opioid analgesics. It has a high degree of analgesic potency (ED50 = 0.0044 mg/kg) and due to its rapid onset and ultra-short duration of action (15 min.) it became a clinically useful addition to the fentanyl family of analgesics. Remifentanil in combination with a hypnotic drug can be administered in relative high doses due to its rapid elimination from the blood plasma. This means, that accumulation does not occur with Remifentanil and its context-sensitive half-life remains at 4 minutes after a 4-hour infusion. Remifentanil is metabolized by non-specific tissue and plasma esterases, which hydrolyses one of the ester groups. The formed Remifentanil acid has 1/4600th the activity of the parent compound. The pharmacokinetics of Remifentanil also offers faster recovery after surgery.



Remifentanil hydrochloride

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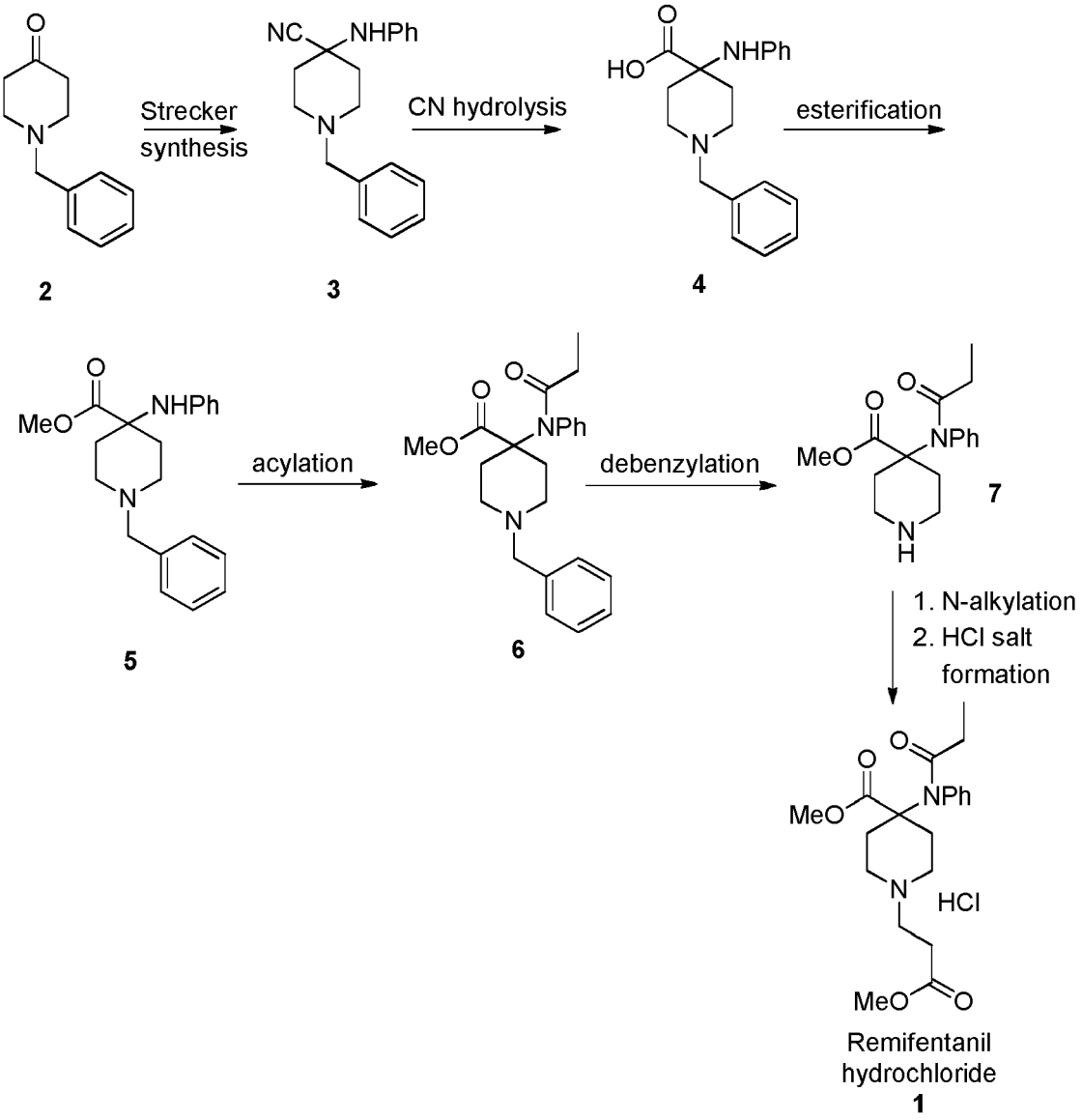
Figure 1 Structure of Remifentanil hydrochloride

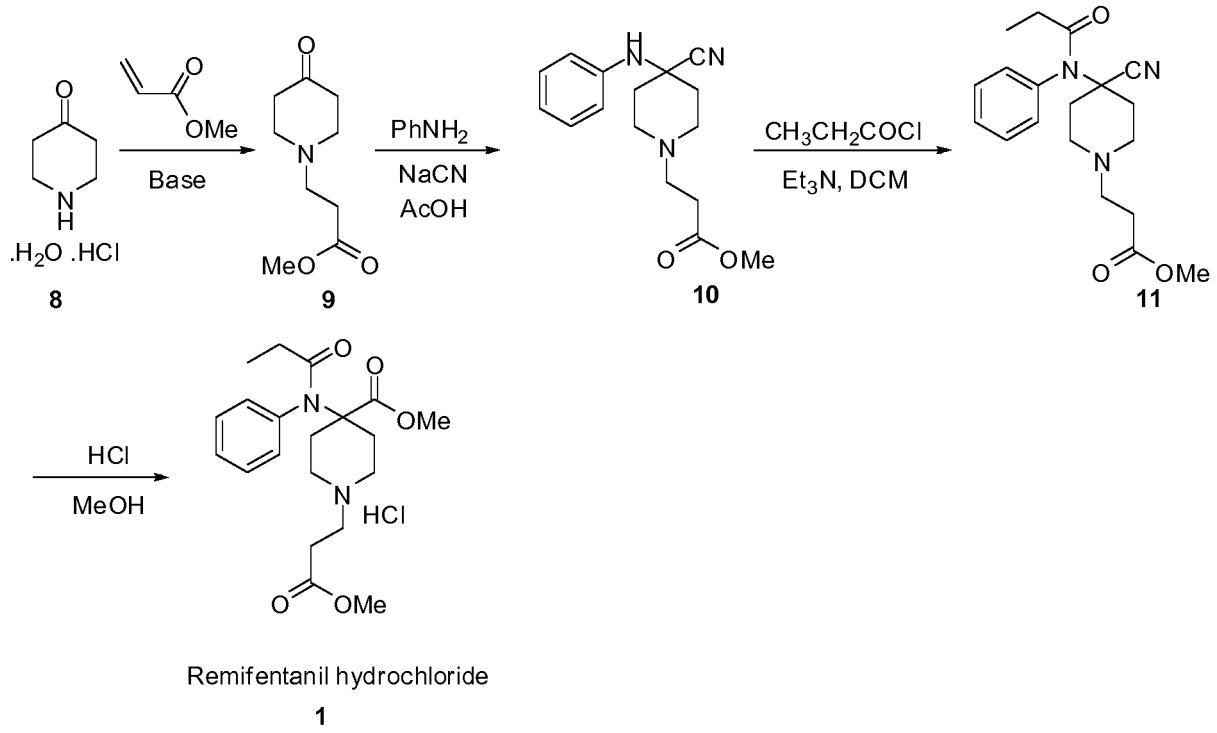
[0003] The preparation of Remifentanil hydrochloride was disclosed in patent EP 0383579 A1 which describes the last two steps of the synthesis shown in scheme 1. Key intermediate **7** is prepared according to literature (P.G.H. Van Daele et al. Arzneim.-Forsh. Drug. Res. 1976, 26, 1521) in 5 steps starting form 1-benzyl-4-piperidone (**2**).



Scheme 1 Synthesis of Remifentanil hydrochloride according to patent EP 0383579 A1

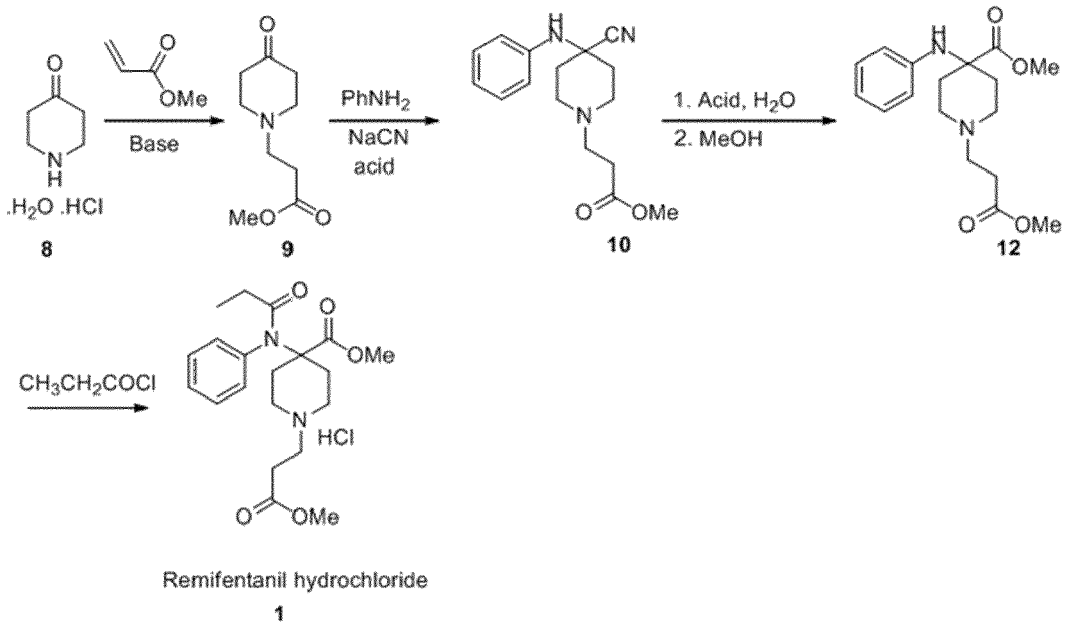
[0004] A 4 step synthesis is described in patent WO 2007144391 (Kern Pharma). Starting material 4-piperidone **8** is alkylated with methyl acrylate followed by the introduction of the aniline function and a nitrile group using Strecker synthesis. Acylation of the aniline nitrogen using propionyl chloride generates the precursor of Remifentanil hydrochloride (**11**). In the last step the nitrile group is converted into a methyl ester using methanol and HCl, thus affording the target molecule.

[0005] Hydrolysation of nitrile groups in this synthesis are with low yields because of the ester group that is partly saponified under the conditions and side products are formed. The intermediates containing a methyl ester function are prone to fast hydrolysis.



Scheme 2 Preparation of Remifentanil hydrochloride according to patent WO 2007144391

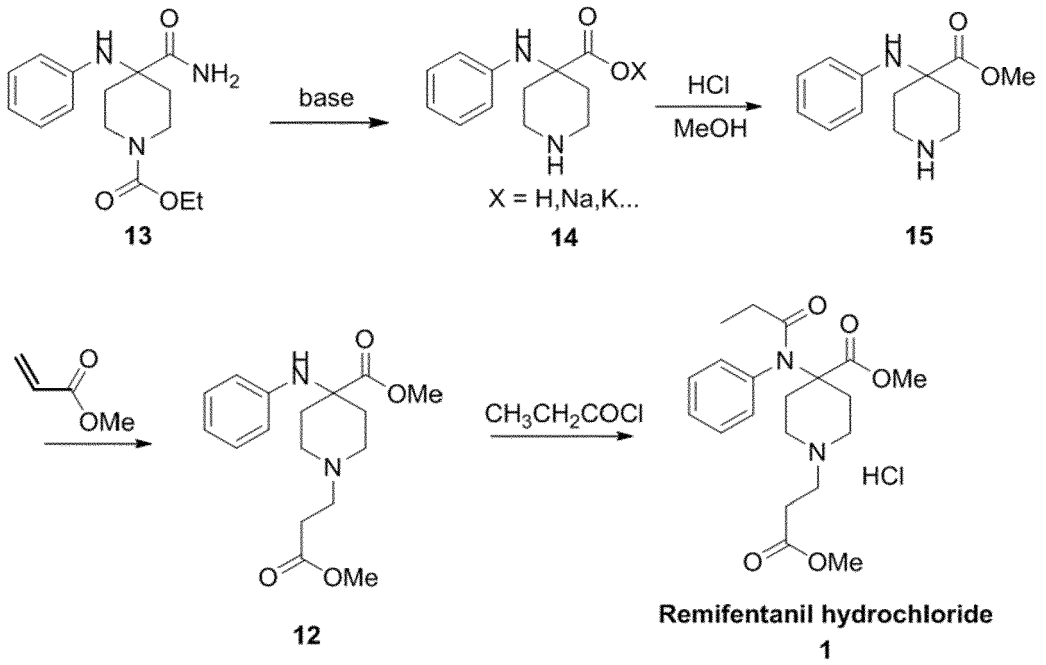
[0006] Patent WO 2007061555 (Mallinckrodt Inc.) made a small alteration in the synthesis of Remifentanil HCl compared to patent WO 2007144391. The nitrile function in compound 10 is first hydrolyzed to an amide which is then converted to a methyl ester. In the final step the propionyl function is introduced. (Scheme 3)



Scheme 3 Synthesis of Remifentanil hydrochloride claimed by patent WO 2007061555

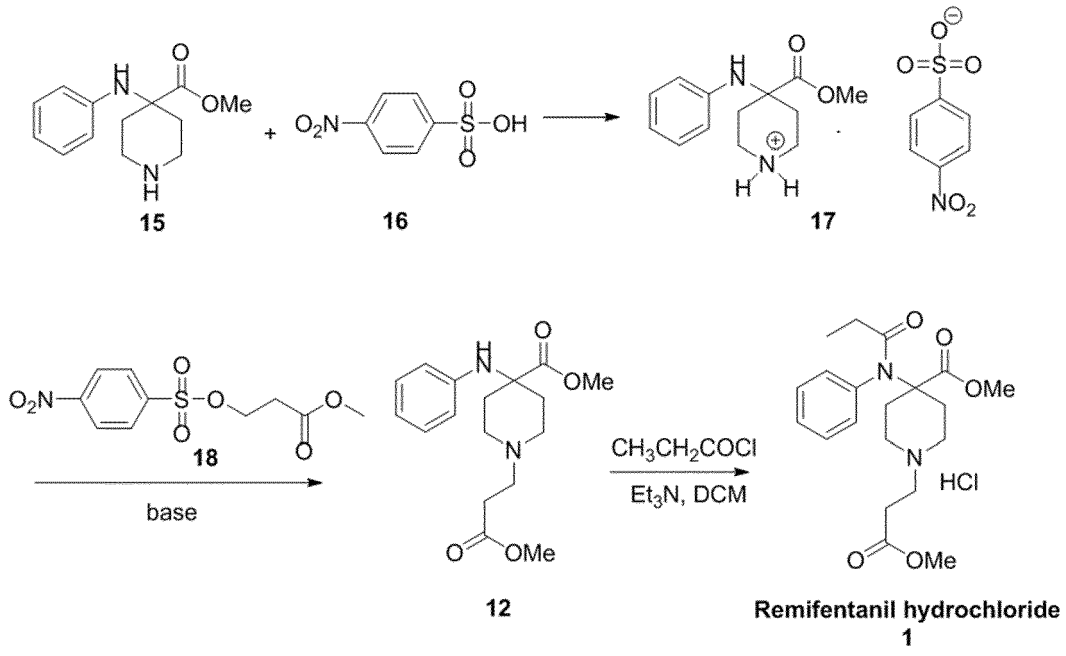
[0007] The synthesis of Remifentanil hydrochloride according to patent WO 2007087164 (Mallincrodt Inc.) starts with 1-(carbethoxy)-4-(phenylamino)-4-piperidine carboxamide, which is hydrolysed to carboxylic acid or carboxylate group

simultaneously with deprotection of the piperidine nitrogen. In the following step the esterification of the carboxylic group with methanol is carried out. Alkylation of the piperidine amine with methylacrylate followed by the acylation of the secondary nitrogen with propionyl chloride generates Remifentanil hydrochloride (Scheme 4).



Scheme 4 Synthesis of Remifentanil hydrochloride claimed by patent WO 2007087164

[0008] All the above mentioned synthetic routes used Michael addition to introduce the methyl propionyl function. In patent WO 2010053944 (Cambrex Charles City, Inc.) methyl 1-benzyl-4-(N-phenylpropionamido)piperidine-4-carboxylate is treated with 4-nitrophenyl sulfonic acid to create nosylate salt **17,** which is then reacted under basic condition with methyl hydroxypropionate activated with a nosylate function (**18**). Acylation of the last intermediate with propionyl chloride gives the final API Remifentanil hydrochloride (Scheme 5).

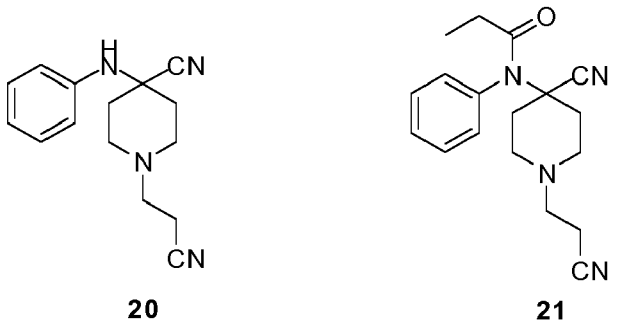


Scheme 5 Synthesis of Remifentanil hydrochloride disclosed in patent WO 2010053944

Description of the invention

1. New compounds

[0009] It has now been found two new intermediates that are useful in the synthesis of Remifentanil. Compound 20 and compound 21.



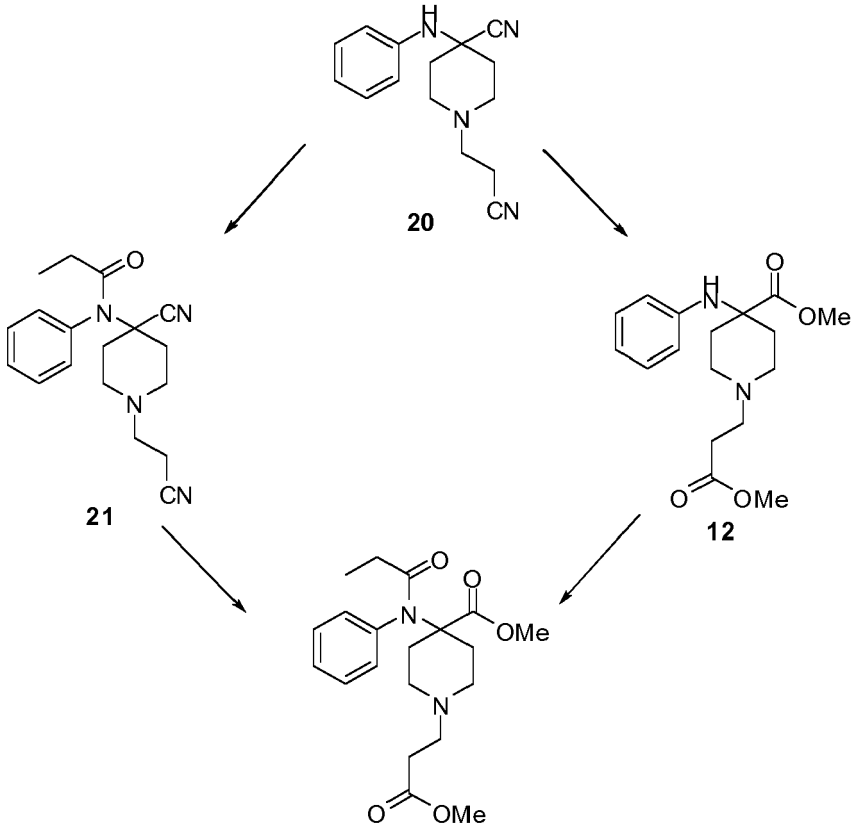
[0010] The use of intermediates containing two nitrile groups has many advantages compared to the synthesis as used so far. For example it gives the opportunity to exclude the Michael addition to the nitrogen side chain in the synthesis, thus deleting the use of alpha-beta unsaturated reagents such as acrylic acid ester in the reaction, which is suspect to show cytotoxic properties.

[0011] The use of intermediates containing two nitrile groups further gives the opportunity to deliberate the ester groups at two parts of the molecule within one single synthesis step, thus increasing the total yield of the total synthesis of Remifentanil.

2. Use of new compound in the synthesis of Remifentanil

[0012] Compound 20 may be used in different ways for the synthesis of Remifentanil.

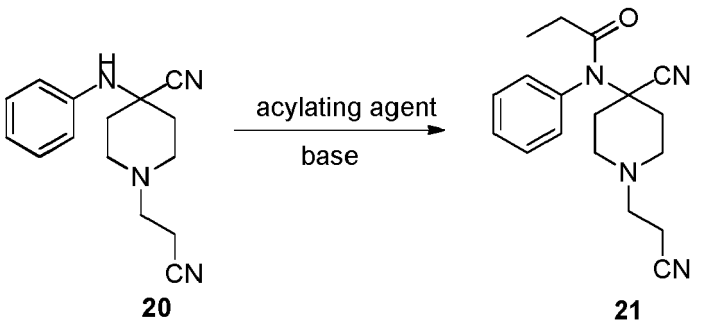
[0013] In one embodiment the compound is converted to the new compound **21,** in another embodiment, compound **20** is transferred to a compound **12,** that was already reported in patent applications as shown above.



3. Use of new compound **20** in the preparation of new compound **21**

[0014] In the first embodiment of the invention the new compound is acylated by an appropriate acylating agent to compound **21.**

[0015] 1-(2-cyanoethyl)-4-(phenylamino)piperidine-4-carbonitrile (**20**) reacts with an acylating agent in presence or without presence of a base to give 1-(2-cyanoethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carbonitrile (**21**, Scheme 9)



Scheme 9 Preparation of remifentanil precursor **21**

[0016] The reaction mixture comprises about 1 molar equivalent to about 10 molar equivalents of acylating agent. In one example the reaction mixture is charged with about 1 to 3 molar equivalent of acylating agent to 1 molar equivalent of 1-(2-cyanoethyl)-4-(phenylamino)piperidine-4-carbonitrile **20.**

[0017] In one embodiment the reaction between compound **20** and acylating agent occurs in the presence of an acid scavenger (base), wherein the reaction mixture comprises about 1 molar equivalent to 3 molar equivalents of the acid

scavenger.

[0018] The temperature of the reaction mixture during reaction ranges from about 0° C to about 80° C. Preferably, the reaction temperature ranges from about 30° C to about 50° C. The reaction mixture is allowed to react up to several days. In one example the reaction time is from about 10 hours to 30 hours.

[0019] In one embodiment the acylating agent is propionic anhydride. In another embodiment the acylating agent is propanoyl chloride. Both reagents show comparable yields in the reaction.

[0020] Examples of solvents used in the reaction mixture and crystallization include solvents that are inert to the reaction occurring in step 3. Examples of such solvents include, but are not limited to acetonitrile, acetone, dichloromethane, chloroform, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, dimethylsulfoxide, tert-butyl methyl ether, diisopropyl ether, ethyl acetate, dichloroethane, benzene, toluene, xylene, 1,4-dioxane, tetrahydrofurane, 2-methyl tetrahydrofurane, methyl ethyl ketone and mixtures thereof. In one example the mixture contains dichloromethane. The compound **20** to solvent ration on wt. basis is about 1:10 to 1:50.

[0021] The acid scavenger can include metal hydrides, hydroxides, carbonates, bicarbonates, amines, and the like.

[0022] After the reaction is completed water and base are added to the reaction to adjust the pH to above 7. Solvent extraction is done with an organic solvent. The solvent is removed under reduced pressure to obtain the crude product. The crude product can be purified by chromatography or recrystallization.

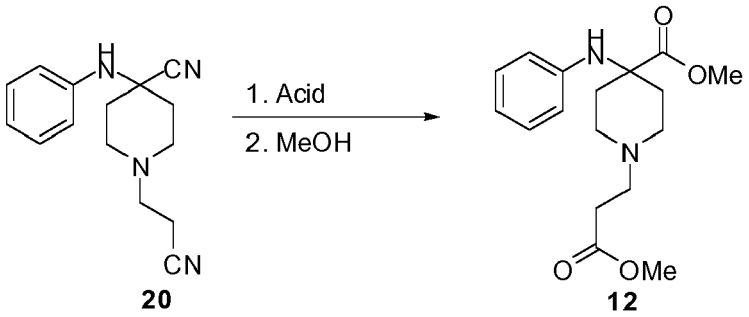
[0023] In one example compound **21** can be dissolved in an organic solvent to which a solution of an acid in a solvent is added to form a salt of compound **21,** which can be isolated by procedures known in the art. Examples of solvents include, but are not limited to acetonitrile, acetone, dichloromethane, chloroform, *N,N*-dimethylformamide, dimethyl sulfoxide, ethyl acetate, dichloroethane, water, benzene, toluene, xylene, methanol, ethanol, isopropanol and mixtures thereof. Examples of acids include hydrochloric acid, hydrobromic acid, methanesulfonic acid, 4-methylbenzensulfonic acid, sulfuric acid, phosphoric acid, citric acid, oxalic acid and the like. Compound 21 is then converted to remifentanil as described below.

[0024] The following table shows the different reagents that have been used for this reaction step.

Solvent	Acylating agent	Base	Crystallization	Yield [%]
Acetonitrile	Propionyl chloride	TEA	IPA	45
Toluene	Propionyl chloride	TEA	IPA	59
chloroform	Propionyl chloride	TEA	IPA	78
Dichloromethane	Propionic anhydride	TEA	IPA	65
Dichloromethane	Propionyl chloride	Pyridine	IPA	62
DMF	Propionyl chloride	TEA	IPA	58
Dichloromethane	Propionyl chloride	TEA	IPA	94
Dichloromethane	Propionyl chloride	TEA	MEK/IPA	89
Dichloromethane	Propionyl chloride	TEA	EtOH	81
Dichloromethane	Propionyl chloride	TEA	acetone	84

4. Use of compound **20** in the preparation of compound **12**

[0025] In another embodiment of the invention the new compound **20** is converted in one step to the known compound **12:**



[0026] The synthesis of compound 12 is a one pot reaction taking place in a single reaction mixture wherein no intermediate amide product is isolated. The reaction may be conducted as described for example in WO2007061555. In a first reaction, compound **20** is hydrolyzed with an acid and water to form an intermediate amide in situ. The reaction mixture can optionally comprise a solvent.

[0027] In one embodiment, the reaction mixture comprises about 3 molar equivalents to about 10 molar equivalents of the acid to 1 molar equivalent of compound **20.** In another embodiment, the reaction mixture comprises about 3 molar equivalents to about 5 molar equivalents of the acid to 1 molar equivalents of compound **20**

[0028] In one embodiment, the reaction mixture temperature is from about -10° C to about 40° C. In another example, the reaction mixture temperature is from about 15° C to about 35°C. In still another example, the reaction mixture temperature is from about 10° C to about 30° C.

[0029] The reaction mixture is permitted to react up to a couple of days. In one example, the reaction is carried out up to about 24 hours. In another example, the reaction time is from about 2 hours to 8 hours

[0030] The acid source can be selected from organic or inorganic acids to adjust the pH of the reaction mixture below about 7. In one embodiment, the acid is selected from acetic acid, hydrochloric acid, sulfuric acid, methansulfonic acid, phosphoric acid, oxalic acid, and the like. In one example, the acid concentration is between 10% and about 99%, preferably between 70% and about 99%, with the balance comprising water. In still another example, the acid is selected from sulfuric acid or methansulfonic acid.

[0031] In one embodiment, the reaction mixture contains a solvent selected from the organic solvents described above for Scheme 2. In one example, the solvent comprises between about 10% to about 99% acid.

[0032] If the reaction takes place under anhydrous conditions, excess amount of alcohol is used as a solvent in the reaction mixture. In one embodiment, the alcohol is an aliphatic alcohol having 1 to 3 carbons.

[0033] In a second step an alcohol is added to the reaction mixture, wherein. The intermediate amide is esterified to form compound **12.**

[0034] In another embodiment, the nitrile compound may be added to a mixture of alcohol and acid in one step to form the corresponding ester 12 via a Pinner-salt.

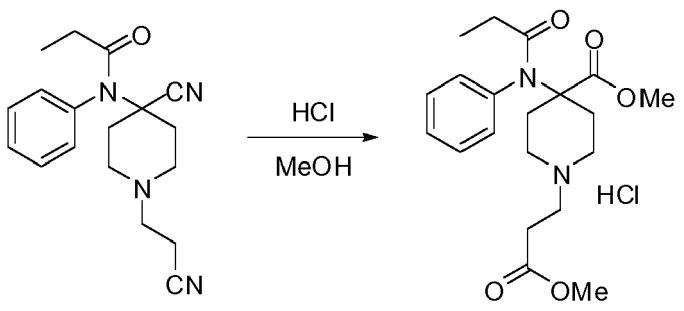
[0035] In one embodiment, about 10 parts to about 50 parts of alcohol are added to the reaction mixture. In one example, about 10 parts to about 20 parts of alcohol are added to the reaction mixture.

[0036] In one embodiment, the reaction mixture temperature is from about -10° C to about 75° C. In another example, the reaction mixture temperature is from about 40° C to about 65° C. The reaction mixture is permitted to react for about 24 hours to about 150 hours. In another example, the reaction time is from about 60 hours to about 100 hours.

[0037] Compound 12 can be isolated by utilizing isolation procedures known in the art such as those described for the above schemes.

5. Use of new compound 21 in the preparation of Remifentanil

[0038] In the final step 1-(2-cyanoethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carbonitrile (**21**) reacts with methanol in acidic conditions to give Methyl 1-(3-methoxy-3-oxopropyl)-4-[phenyl(propanoyl)amino] piperidine-4-carboxylate hydrochloride (Remifentanil hydrochloride, **1**)



21

Remifentanil hydrochloride
1

Scheme 10 Preparation of Remifentanil hydrochloride from compound **21**

[0039] In one embodiment the reaction mixture comprises of about 5 molar equivalent to about 20 molar equivalent of hydrochloric acid to 1 molar equivalent of 1-(2-cyanoethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carbonitrile **21**

[0040] In one embodiment methanol is used as solvents and acetone, acetonitrile, methanol, ethanol, isopropanol, methyl ethyl ketone are used as solvents for crystallization. The compound **21** to solvent ration on wt. basis is about 1:2 to 1:10.

[0041] The temperature of the reaction mixture during reaction ranges from about 0° C to about 50° C. The reaction mixture is allowed to react up to several days. In one example the reaction time is from about 10 hours to 30 hours.

[0042] Compound **1** can be isolated by using isolation procedures known in the art.

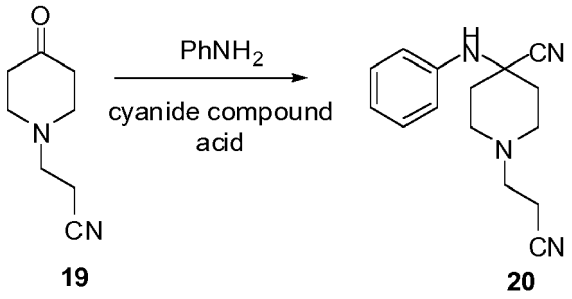
[0043] The following table shows the different reagents that have been used for this reaction step.

HCl in Methanol	Temperature	Crystallization	Yield [%]
8 : 1	r.t	IPA	54
10 : 1	r.t.	IPA	63
8 : 1	40°C	1. IPA 2. MEK:IPA	47
10 : 1	40°C	Acetone:MeOH	54
8 : 1	reflux	MEK:IPA (2:3)	64
10 : 1	40°C	EtOH	51
10 : 1	40°C	MeOH	72

6. Preparation of new compound **20**

[0044] Compound **20** may be synthesized in one step from the commercially available 3-(4-Oxopiperidin-1-yl)propanenitrile **19** with phenylamine in the presence of a cyanide compound and an acid.

[0045] Scheme **8** below illustrates the process wherein 3-(4-oxo-piperidine-1-yl)propanenitrile reacts with aniline and a cyanide containing reagent in the presence of an acid to give 1-(2-cyanoethyl)-4-(phenylamino)piperidine-4-carbonitrile **20**



Scheme 8 Preparation of intermediate **20**

[0046] In one embodiment the reaction mixture comprises of about 1 molar equivalent to about 3 molar equivalents of aniline, about 1 molar equivalent to about 3 molar equivalents of cyanide compound and about 2 molar equivalents to 5 molar equivalents of acid to 1 molar equivalent of **19.** Preferably, the reaction mixture is charged with about 1 to 1.5 equivalent of aniline, about 1 to 1.5 equivalent of cyanide compound and about 3-4 equivalent of acid to 1 equivalent of 3-(4-oxo-piperidine-1-yl)propanenitrile. The compound **19** to solvent ration on wt. basis is about 1:5 to 1:20.

[0047] The temperature of the reaction mixture during reaction ranges from about 0° C to about 80° C. Preferably, the reaction temperature ranges from about 20° C to about 60° C. The reaction mixture is allowed to react up to several days. In one example the reaction time is from about 2 hours to 5 hours.

[0048] The non-limiting examples of cyanide compounds are sodium cyanide, potassium cyanide, trimethylsilyl cyanide, hydrogen cyanide and the like.

[0049] Due to economic reasons, sodium cyanide is preferred.

[0050] The acid may include any organic and inorganic acid to adjust the pH below 7. Non-limiting examples of acids include acetic acid, hydrochloric acid, sulfuric acid, phosphoric acid, oxalic acid and the like. In one embodiment acetic acid is utilized to adjust the pH below 7.

[0051] Examples of solvents used in the reaction mixture include, but are not limited to acetonitrile, dichloromethane, chloroform, *N,N*-dimethylformamide, dimethylsulfoxide, ethyl acetate, dichloroethane, water, benzene, toluene xylene, methanol, ethanol, isopropanol and mixtures thereof.

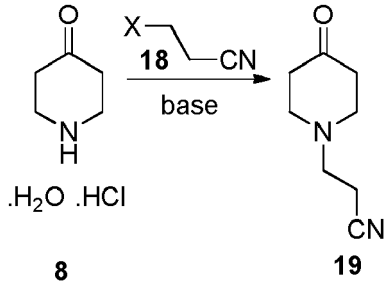
[0052] Compound **20** can be isolated through solvent extraction or precipitation from the reaction mixture. Compound **20** can be further purified by using purification procedure known in the art. In one example compound **20** can be dissolved in an organic solvent to which a solution of an acid in a solvent is added to form a salt of compound **20,** which can be isolated by procedures known in the art. Examples of solvents include, but are not limited to acetonitrile, acetone, dichloromethane, chloroform, *N,N*-dimethylformamide, dimethyl sulfoxide, ethyl acetate, dichloroethane, water, benzene, toluene, xylene, methanol, ethanol, isopropanol and mixtures thereof. Examples of acids include hydrochloric acid, hydrobromic acid, methanesulfonic acid, 4-methylbenzensulfonic acid, sulfuric acid, phosphoric acid, citric acid, oxalic acid and the like.

[0053] The following table shows the different reagents that have been used for this reaction step.

Solvent	Cyanide compound	Acid	Yield %
MeOH	NaCN	AcOH	79
DCM	NaCN	AcOH	65
MeTHF	NaCN	AcOH	65
toluen	NaCN	AcOH	53
ACN	NaCN	AcOH	82
MeOH/H_2O	NaCN	AcOH	50
H_2O	NaCN	AcOH	78
H_2O	KCN	AcOH	62
H_2O	NaCN	HCl	51
H_2O	NaCN	H_2SO_4	45

7. Preparation of compound **19**

[0054] Scheme 7 below illustrates the reaction wherein 4-piperidone monohydrate hydrochloride reacts with propionitrile derivative **18** to give 3-(4-oxo-piperidine-1-yl)propanenitrile



8 **19**

X: Cl, Br, I, OMs, OTs

Scheme 7 Preparation of intermediate **19** from 4-piperidone

[0055] In one embodiment compound **8** is mixed in a reaction mixture with propionitrile derivative **18** with a leaving group in position 3 in the presence of a solvent and a base to form intermediate **19.** The reaction mixture comprises of about 1 molar equivalent to about 6 molar equivalents of **18** and about 1 molar equivalent to about 6 molar equivalent of base to 1 molar equivalent of **8.** Preferably, the reaction mixture is charged with about 2 to 3 equivalent of **18** and about 2 to 4 equivalent of base to 1 equivalent of 4-piperidone monohydrate hydrochloride. The compound **8** to solvent ratio on wt. basis is about 1:3 to 1:20.

[0056] The temperature of the reaction mixture during reaction ranges from about 0° C to about 80° C. The reaction mixture is allowed to react from about 6 h to about 48 h. In one example the reaction time is from about 18 hours to 24 hours.

[0057] Examples of propionitrile derivative **18** include 3-chloropropionitrile, 3-bromopropionitrile, 3-iodopropionitrile, 2-cyanoethyl methanesulfonate, 2-cyanoethyl 4-methylbenzenesulfonate.

[0058] Examples of the base include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, metal alkoxides, metal amides, metal hydrides and amines.

[0059] Examples of solvents used in the reaction mixture include, but are not limited to acetonitrile, acetone, methyl ethyl ketone, dichloromethane, chloroform, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, dimethyl sulfoxide, ethyl acetate, dichloroethane, benzene, toluene, xylene, tetrahydrofuran, 2-methyl tetrahydrofuran and mixture thereof.

[0060] In one embodiment compound **19** can be isolated through solvent extraction and isolation procedure known in the art. Such isolation can include evaporation of solvent to recover the crude oily product.

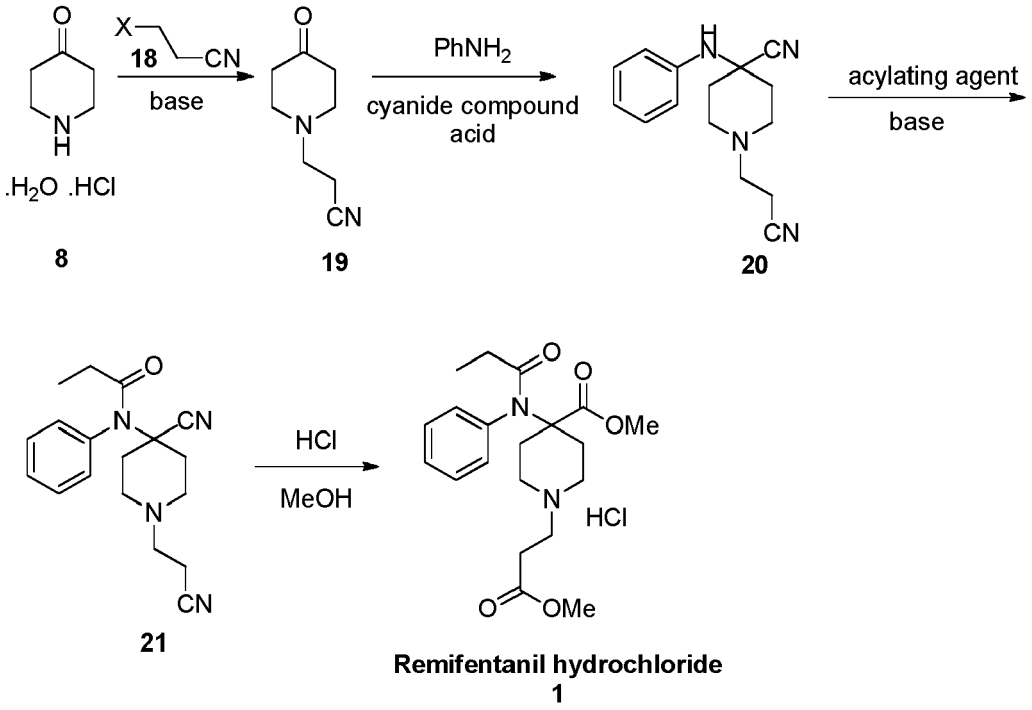
[0061] In some examples compound **19** can be further purified by distillation or chromatography. In one example compound **19** can be dissolved in an organic solvent to which a solution of an acid in a solvent is added to form a salt of compound **19,** which can be isolated by procedures known in the art. Examples of solvents include, but are not limited to acetonitrile, acetone, dichloromethane, chloroform, *N,N*-dimethylformamide, dimethyl sulfoxide, ethyl acetate, dichloroethane, water, benzene, toluene, xylene, methanol, ethanol, isopropanol and mixtures thereof. Examples of acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, oxalic acid and the like.

[0062] The following table shows the different reagents that have been used for this reaction step.

Solvent	Base	Alkylating agent	Yield [%]
DCM	K_2CO_3	3-chloropropionitrile	75
acetone	TEA	3-bromopropionitrile	76
MEK	NaOH	3-bromopropionitrile	88
MEK	K_2CO_3	3-chloropropionitrile	85
Acetone	K_2CO_3	3-bromopropionitrile	69
MeOH	K_2CO_3	2-cyanoethyl methanesulfonate	68

8. Use of the new compounds in the Synthesis of Remifentanil

[0063] Following the above mentioned a new method for the preparation of Remifentanil hydrochloride is described in the present invention. We have found that both methyl ester groups present in Remifentanil hydrochloride can be obtained from nitrile functions in the final step. The synthesis starts form 4-piperidone.H_2O.HCl and the target API is obtained after 4 reaction steps (Scheme 6).



Scheme 6 Preparation of Remifentanil hydrochloride described in the present invention

EXAMPLES

[0064] The following examples are provided in order to more fully illustrate the present invention.

Example 1

Synthesis of 3-(4-oxopiperidin-1-yl)propanenitrile

[0065] 5.10 mL (2 eq.) of 3-chloropropionitrile, 5.0 g of 4-piperidone monohydrate hydrochloride and 13.5 g (3 eq.) of K2CO3 were suspended in 40 mL of methyl ethyl ketone. The mixture was heated to 80°C for 18 h. The solids were filtered off and the filtrate was concentrated under vacuum. Then it was dissolved in 30 mL of distilled water and extracted with ethyl acetate. The organic phase was dried over Na2SO4 and concentrated under vacuum: 4.21 g of 3-(4-oxopiperidin-1-yl)propanenitrile as a yellow liquid was obtained.

Example 2

Synthesis of 1-(2-cyanoethyl)-4-(phenylamino) piperidine-4-carbonitrile

[0066] 1.69 g (1.05 eq.) of NaCN dissolved in 4.5 mL of distilled water was added dropwise (RT, ~30 min.) to a stirred solution of 5g of 3-(4-oxopiperidin-1-yl)propanenitrile, 4.8 mL (1.6 eq.) of aniline and 4.9 mL (2.6 eq.) of acetic acid in 25 mL of methanol. The solution was heated to 60°C for ca. 20 h. and then cooled down to 0°C. NaOH solution (33% w/v) was added dropwise while white precipitate was being formed (ca. 7 mL). Distilled water was added (10 mL) and the suspension was stirred at 0°C for 6 h. The precipitate was filtered off, washed with H_2O:MeOH (1:1) mixture and left to dry. Yield: 6.5g (78%) of off-white powder.

Example 3

Synthesis of *N*-(4-cyano-1-(2-cyanoethyl)piperidin-4-yl)-*N*-phenylpropionamide

[0067] 12.4 mL (3 eq.) of propionyl chloride was added dropwise to a cooled and stirred solution of 12g of 1-(2-cyanoethyl)-4-(phenylamino) piperidine-4-carbonitrile in 120 mL of dichloromethane. Shortly, white precipitate formed. The mixture was refluxed overnight for ca. 20 h. and then allowed to reach RT. 6.5 mL (1 eq.) of triethylamine was added dropwise. The mixture turned transparent and gradually opaque again. After stirring at RT overnight (20 h.), 120 mL of distilled water was added. The separated organic phase was washed with 120 mL of sat. Na2CO3 solution, 120 mL of brine, dried over Na2SO4 and concentrated under vacuum: 8.2g of crude light-brown matter was obtained. The crude product was crystallized from 40 mL of isopropanol. The precipitate was filtered off, washed with cold isopropanol and left to dry. Yield: 7.25g (49%) of white powder.

Synthesis of Remifentanil HCl

Example 4

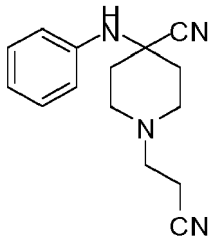
[0068] 30 mL (15 eq.) of 35% HCl solution in methanol was added to 5g of N-(4-cyano-1-(2-cyanoethyl)piperidin-4-yl)-N-phenylpropionamide and the mixture was stirred at room temperature. After 20 h., 5 mL of methanol was added and the suspension was stirred for additional 5 h. at room temperature. It was then filtered, the precipitate was washed with 5 mL of cold isopropanol and left to dry. The crude product contains an inorganic residue (NH4Cl) which can be filtered off during crystallization. 5.3g of the crude product was suspended in 75 mL of isopropanol (13-15 mL/g) and refluxed for 15 min. While hot, the inorganic solid was filtered off and washed with 20 mL of hot isopropanol. The filtrate was refluxed again for 5 min., allowed to reach RT and cooling to 5°C for 2 h. The crystal was filtered off, washed with isopropanol and left to dry. Yield: 2.18g of white powdery crystals.

Example 5

[0069] 30 mL (15 eq.) of 35% HCl solution in methanol was added to 5g of N-(4-cyano-1-(2-cyanoethyl)piperidin-4-yl)-N-phenylpropionamide and the mixture was stirred at room temperature. After 20 h., 5 mL of methanol was added and the suspension was stirred for additional 5 h. at room temperature. It was then filtered, the precipitate was washed with 5 mL of cold isopropanol. The crude product was slowly added to 80 mL of stirred sat. Na2CO3 solution. The product was extracted with 2x40 mL of ethyl acetate. The organic phases were combined, dried over Na2SO4 and concentrated under reduced pressure. The obtained remifentanil base was dissolved in 15 mL of methanol, cooled to 5°C, and slowly added gaseous HCl (1.5 eq.). The precipitated hydrochloride salt was filtered off. Yield: 4.5 g of white powdery crystals.

Claims

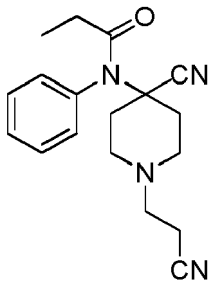
1. A compound of the formula 20 and its salts:



20

2. Use of compound **20** for the synthesis of Remifentanil (**1**).

3. Use of compound **20** according to claim 2 wherein compound **20** is first converted to compound **21.**



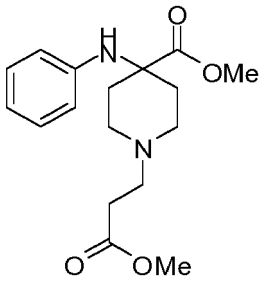
21

4. Method according to claim 3, where the acylating agent is propion anhydride or propionyl chloride

5. Method according to claim 4, wherein an acid scavenger selected from triethylamine, morpholine, piperidine, pyridine or other organic base is used.

6. Method according to claim 3 wherein the compound **21** is converted to Remifentanil (**1**)

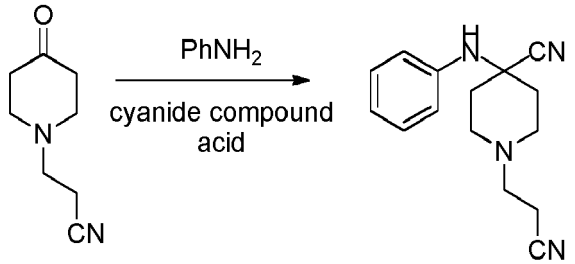
7. Use of compound **20** for the synthesis of Remifentanil according to claim 2 wherein compound **20** is first converted to compound **12.**



12

8. Method according to claim 7 wherein the compound **12** is converted to Remifentanil (**1**)

9. Method for the preparation of a compound according to claim 1 wherein the compound is prepared by reaction of compound **19** with phenylamine in the presence of a cyanide compound.



19 20

10. Method according to claim 9 wherein the cyanide compound is sodium cyanide.

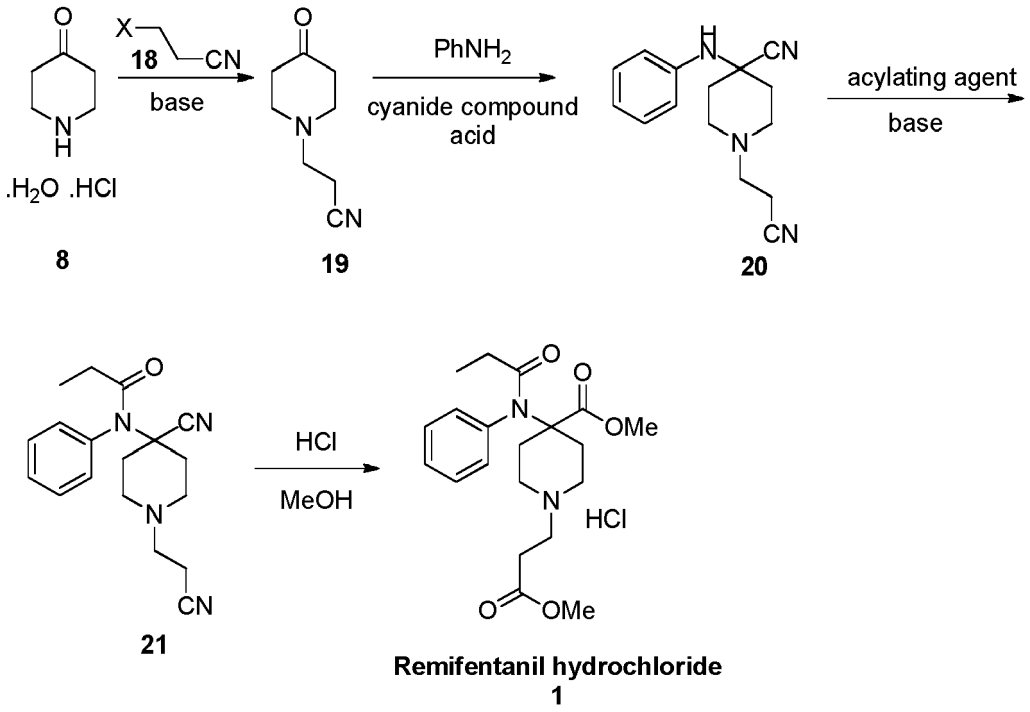
11. Method for the preparation of compound **19** wherein the compound is prepared by alkylating 4-piperidone monohydrate hydrochloride with an appropriate alkylating agent in the presence of a basic catalyst

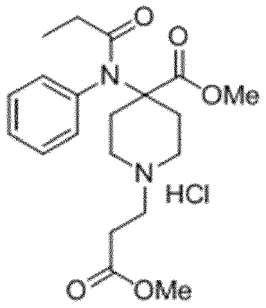
12. Method according to claim 11 wherein the appropriate alkylating agent is 3-chloropropionitrile, 3-bromopropionitrile, 3-iodopropionitrile, 2-cyanoethyl methanesulfonate, 2-cyanoethyl 4-methylbenzenesulfonate,

13. Method according to claim 12 wherein a basic catalyst is sodium or potassium carbonate, sodium hydrogen carbonate, sodium or potassium hydroxide, sodium amide, potassium terc-butoxide, sodium ethoxide,

14. Method according to claim 13 wherein the used solvent is acetone, methyl ethyl ketone, isopropanol, acetonitrile, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, tetrahydrofuran, 2-methyl tetrahydrofuran,

15. Use of a compound according to claim 1 for the synthesis of remifentanil hydrochloride according to the following scheme:





Remifentanil hydrochloride

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EUROPEAN SEARCH REPORT

Application Number
EP 18 20 2878

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A,D	WO 2007/144391 A1 (KERN PHARMA S L [ES]; CERVELLO PAGES JORGE [ES]; CANTO VALLVERDU MARIA) 21 December 2007 (2007-12-21) * claims 1-17; examples 1-3; *	1-15	INV. C07D211/66
A,D	WO 2007/061555 A1 (MALLINCKRODT INC [US]; CHENG BRIAN [US]) 31 May 2007 (2007-05-31) * claims 1-34; Schemes 1-8; *	1-15	

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C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	12 December 2018	Wolf, Claudia

CATEGORY OF CITED DOCUMENTS

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